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Chemetals Incorporated
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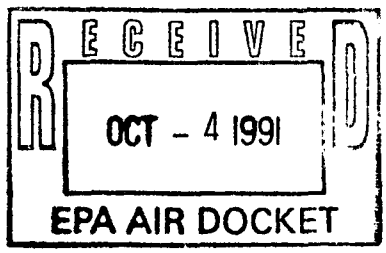
CHEMETALS

October 4, 1991



Public Docket A-91-46
Air Docket (LE-131)
U.S. Environmental Protection Agency
Room M-1500
401 M Street, Southwest
Washington,DC 20460

RE: Comments of Dr. Albert C. Kolbye on the waiver request of Ethyl Corporation for use of HiTEC 3000 in unleaded gasoline in the United States

Dear Sir/Madam:

Chemetals, Inc. submits the attached comments previously submitted by Dr.Albert C. Kolbye to Public Docket A-90-16. Please include these pertinent comments in the public record to be considered by the EPA in evaluating the merits of HiTEC 3000.

Sincerely,

Francis J. Keenan
Vice President-Technology

cc: Mary T. Smith- EPA

CQC

Chemetals Quality Commitment
Continuous Improvement

KOLBYE ASSOCIATES
EVALUATION OF PROPOSED USE OF MMT

Kolbye Associates
7313 Helmsdale Road
Bethesda, MD 20817
July 20, 1990

INTRODUCTION:

This is a brief report of our scientific analysis and evaluation of the proposed use of HiTech 3000 as a manganese additive to gasoline.

We have conducted an extensive search of recently published scientific literature and critically evaluated these reports in conjunction with previous knowledge of the potential toxicity of various manganese-containing compounds.

OUR OPINION IN SUMMARY

We have no objection to the proposed use of MMT nor do we believe that any significant health problems will result from its use in this manner. In addition, future scientific research will continue to develop additional knowledge about traces of environmental manganese in various media such as ambient air. Any potentional hazard can be monitored continuously without any risk to public health. We see no reason whatsoever to deny the waiver for MMT.

1) MANGANESE IS ESSENTIAL TO HUMAN HEALTH.

There can be no question of the nutritional importance of manganese in the diet. Manganese is an essential co-factor and component of many enzymes, notably in the mitochondria. Deficiencies are well recognized in laboratory animals. In humans there is corresponding evidence but to a lesser degree of documentation. Obviously, the human body, through biological evolution, requires manganese and is experienced in metabolizing manganese compounds ingested in the diet. Variations of absorption and excretion exist, when infants, pregnant women, and older adults are compared. However, the only human disease problems attributed to manganese were caused by occupational inhalation exposures for protracted time-periods to high concentrations of manganese oxides (at levels of tens of milligrams per cubic meter of air).

2) MANGANESE DOES NOT POSE A PUBLIC HEALTH RISK AT AMBIENT LEVELS.

Manganese is the 12th most common element of the earth's crust. Airborne dust from ground soil is a major source of pulmonary exposure for humans, as is inhalation of air near ocean spray. There are many data on airborne levels of manganese compounds. In a recent Canadian report (1988),

urban levels were reported on the average to range from 65 nanograms per cubic meter to 166. In similar fashion both fresh water and salt water contain appreciable levels of manganese ranging from low to high micrograms per liter. Appreciable levels of manganese compounds occur in many foods notably certain grains and vegetables. It is estimated that humans ingest, on the average, between 4 and 9 milligrams of manganese per day in their diets. We can see that the most substantial sources of human exposure to manganese are dietary and far greater than those usually involved with inhalation. It is true that manganese, when inhaled and absorbed into the blood stream, can follow different pathways of distribution in the body. Most, however, will go to the liver within a short time and be metabolized and excreted. Some may directly enter the brain and here there is evidence of a longer biological half-life. However, the question of neurotoxicity clearly depends on dose. There is strong evidence that only very high concentrations of manganese in inhaled air for protracted periods of time are potentially toxic to brain cells. The ambient air exposures to manganese arising from the proposed use of MMT are infinitesimal by comparison and cannot by any justification from all presently available evidence, be used as a basis to prohibit the usage of MMT.

3) MANGANESE IS EXCRETED FROM THE HUMAN BODY.

Dietary manganese is poorly absorbed, usually 4 percent at most. Inhaled manganese may be absorbed to a greater extent through the alveolar membrane, provided that prerequisite conditions are fulfilled. When high concentrations are involved in inhaled air, occupational diseases have been observed. The same diseases have never been observed in relation to low concentrations of manganese in inhaled air. Low concentrations of manganese of inhaled air contribute very little to the body burden of manganese in most human beings. Homeostatic mechanisms exist in the body to facilitate and regulate manganese excretion. These mechanisms are not disturbed by the very slight airborne exposures that might occur from time to time.

4) MANGANESE IS NOT A KNOWN CARCINOGEN.

Various relatively short-term tests have been performed on a range of manganese compounds with no alarming results. It is noteworthy that after two year exposures of monkeys to inhaled manganese oxide, no precancerous or cancer lesions were reported by the authors (Bird). In passing, it should be noted that any compound given at toxic doses to laboratory animals has a greater likelihood of facilitating the

expression of spontaneously arising cancers. The available epidemiological evidence from miners and factory workers does not raise any suspicion of an increased risk for cancer.

5) MANGANESE IS ONLY NEUROTOXIC TO HUMANS AT HIGH MILLIGRAM INHALATION EXPOSURE LEVELS.

As indicated earlier in this document, only at very high and prolonged inhalation exposures (tens of milligrams per cubic meter of air) has there been documented epidemiological evidence of human disease. Two manifestations occur, one being neurotoxicity resembling Parkinsonism and the other being pneumonitis. These air concentrations involved are many orders of magnitude higher than those anticipated by worst case estimates of additional inhalation exposures caused by use of MMT.

6) OCCUPATIONAL SAFETY INHALATION STANDARDS ARE ORDERS OF MAGNITUDE GREATER THAN PRESENT OR EXPECTED AMBIENT AIR LEVELS.

The present TWA limits recommended by ACGIH and set as a ceiling limit by OSHA for manganese oxide compounds and dust in air in a work setting for an 8 hour day are 5 milligrams per cubic meter. There is no evidence that prolonged and

repetitive inhalation exposures of humans to this concentration of manganese oxides in air has caused any demonstrable recognized health problem. This judgement was arrived at by many scientists acting independently and jointly on various committees, after extensive evaluations of all available scientific evidence concerning occupational hazards to inhaled manganese oxides.

7) THE TOXICITY OF MANGANESE IS DIFFERENT FROM AND NOT RELATED TO THE TOXICITY OF LEAD.

Clearly, lead compounds have no known useful biological functions and have been reported by many epidemiologists and biomedical scientists to cause a spectrum of adverse health effects even at relatively low levels of human exposure. Two major sources of excessive exposure to lead exist: 1) the ingestion of lead-containing paint, and 2) lead in certain foods which previously occurred at very substantial levels especially in certain canned foods. Lead toxicity is determined by the unique characteristics of each particular compound of lead. The same is true for each and every chemical compound in the world. Certain lead salts are absorbed, slowly excreted and can cause brain and kidney damage. While the body has certain mechanisms to detoxify and

excrete lead, they are not remarkably efficient. This is probably because lead is not an essential element for body function; to the contrary, it is a very effective biological poison.

Manganese, only when inhaled in excessive amounts, causes a much more specific pattern of neurotoxic damage. This probably reflects overload beyond normal capabilities of cells to use manganese constructively. There are indications that the trivalent form of manganese is a powerful oxidant, whereas the normal function of divalent manganese is as an antioxidant. One cannot say that there is a biologically required or normal level of lead in the body. One can say that manganese is required for normal body function and only becomes toxic to brain when excessive amounts are inhaled over prolonged periods of time.

8) THE USE OF HAIR SAMPLING TECHNIQUES TO ESTIMATE HUMAN EXPOSURE TO MANGANESE HAS NOT BEEN VALIDATED.

Among experienced scientists, there is concern about the accuracy with which residues of various compounds are measured in hair and whether or not they truly reflect the past pattern of human exposure. This is because direct exposure of hair to a variety of compounds contained in air or in various

cosmetics and shampoos may confound interpretation. This is particularly true with regard to manganese because of its common occurrence in airborne dust which is deposited on body surfaces, including hair. Validation studies on this topic have been inadequate. More importantly, there are data to indicate that such findings misrepresent the body burden of manganese in humans. Quantitative analyses of 24-hour urine excretion or blood levels are likely to be more accurate, although these need further validation also.

9) WHILE DEFICIENCIES Of DIETARY INTAKES OF IRON AND CALCIUM INCREASE MANGANESE ABSORPTION, THEY ARE NOT DIRECTLY RELEVANT TO THE ISSUE INVOLVED HERE.

Many factors influence the absorption through the gastrointestinal tract of dietary components such as divalent cations. These include among others, manganese, iron, and calcium. Some exist in different states of valency. Other dietary components such as ascorbic acid also influence absorption. Iron-deficient humans or those with a propensity to absorb higher amounts of iron such as pregnant women, infants, and people with hemochromatosis will absorb higher amounts of iron than normal. By analogy, they are likely to absorb higher amounts of manganese in the diet if under

similar circumstances. These observations are largely irrelevant to the present issue involving MMT, because inhalation exposure to manganese follows different characteristics, if in fact, the inhaled manganese is absorbed through the alveolar membrane into the blood stream. It is to be expected that a significant portion of inhaled manganese will be adsorbed on other particulates and expelled by ciliary action back to the oropharynx and swallowed where it then is treated by the body as dietary manganese. As such, very little will be absorbed through the gastrointestinal tract under any set of conditions. Persons with higher than normal absorption may absorb relatively higher amounts of manganese than do most people, but most likely it will be readily excreted from the body. We see no problem in this regard as far as the proposed use of MMT is concerned.

CONCLUSIONS

Manganese is required in the diet as an essential nutrient for human health. It is usually readily excreted from the human body. It is not a known carcinogen. Its toxicity is unrelated to lead. Only when humans are exposed by inhalation for prolonged periods of time to air concentrations in the tens of milligrams per cubic meter of air, has disease occurred. Manganese does not pose a public

health risk at ambient concentrations in air, which in turn will not be significantly increased at all by the proposed use of MMT. Occupational safety standards permit orders of magnitude greater exposures to inhaled manganese than could ever under any circumstances be expected from the proposed use of MMT.

BIBLIOGRAPHIC REFERENCES

This report has been prepared after an extensive review of the worldwide literature on manganese, including both scientific publications and governmental commissioned reports. The scientific literature concerning nutritional aspect of manganese has been extensively reviewed, as has all available information on manganese toxicity.

The latter include review of EPA's Health Assessment Document, the Canadian Report, various publications by Davis, Donaldson, Gottschalk, Silbergeld, and many other reports. This database is too extensive for us fully document at this time, but any reader requiring further information as to sources is asked to telephone area code 301/320-2900.

CURRICULUM VITAE

ALBERT CHRISTIAN KOLBYE, JR., M.D., M.P.H., J.D.
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EDUCATION:

William Penn Charter School Philadelphia, Pennsylvania	H.S.	1953
Harvard College Cambridge, Massachusetts (Pre-Med, Pre-Law and Geology)	A.B.	1957
Temple University School of Medicine Philadelphia, Pennsylvania	M.D.	1961
University Hospitals Madison, Wisconsin (Internship - Mixed Medicine)		1962
School of Hygiene and Public Health The Johns Hopkins University Baltimore, Maryland	M.P.H.	1965
The School of Law University of Maryland Baltimore, Maryland	J.D.	1966
Federal Executive Institute Charlottesville, Virginia		1974

LICENSURES:

To Practice Medicine - State of Maryland since 1962
To Practice Law - Maryland and District of Columbia since 1967
Board Certification in Preventive Medicine and Public Health

PROFESSIONAL BACKGROUND:

Internship, University of Wisconsin, Madison - 1962
Residency, Maryland State Department of Health - 1964
United States Public Health Service, Commissioned Corps - 1962-1982:

Heart Disease Control Program - 1962-1966
Staff Director, Smoking & Health Program - 1967-1968
Staff Director, Secretary's Commission on Pesticides - 1969
Deputy Director, Bureau of Foods, FDA - 1970-1972
Associate Bureau Director for Toxicological Sciences, Bureau of Foods, FDA - 1972-1982
Assistant Surgeon General (07) USPHS - 1971-1982

President - The Nutrition Foundation, Inc. 1982-1984
Director - Kolbye Associates 1984 to Present
Past President - International Society of Regulatory Toxicology & Pharmacology 1987-1988

FELLOWSHIPS AND MEMBERSHIPS:

Fellow of:
American Academy of Clinical Toxicology
American Public Health Association
American College of Legal Medicine
American College of Preventive Medicine
International Academy of Environmental Safety

Co-Editor:
Regulatory Toxicology and Pharmacology
Academic Press

Member of:
American Medical Association
American Bar Association
Maryland State Bar Association
Maryland Medical Chirurgical Society
Society of Toxicology
Environmental Mutagen Society
Society for Epidemiologic Research
Society of Ecotoxicology and Environmental Safety
New York Academy of Sciences
Toxicology Forum
Society for Preventive Oncology
International Commission for Protection Against Environmental Mutagens and Carcinogens

CHAIRMANSHIPS OR
STAFF DIRECTORSHIPS:

The Surgeon General's Reports to Congress on the Consequences of Smoking - 1967, 1968 and 1969
The Secretary's Commission on Pesticides and Their Relationship to Environmental Health, DHEW - 1969
Secretary's Representative to the Interagency Pesticide Agreement - 1970

The Health Hazards of Mercury, DHEW - 1971

Health Hazards Evaluation Board, Bureau of Foods, Food and Drug Administration - 1972-1982

Research in Human Subjects, FDA - 1972-1982

Interagency Epidemiological Working Group on Saccharin - 1976-1980

Interagency Working Group on Mechanically Deboned Meat, U.S. Department of Agriculture - 1976-1977

WHO Scientific Consultant for Preparation of Environmental Health Criteria for Nitrates, Nitrites, and N-Nitroso Compounds, Environmental Health Criteria 5, WHO Geneva - 1977

FD&C Red No. 40 Working Group - 1976-1981

Subcommittee 4 (Regulatory and Legislative) International Commission for Protection Against Environmental Mutagens and Carcinogens - 1978-1982

Interagency Working Group on Saccharin Epidemiology

Interagency Working Group on Nitrite Research

RECENT POSITIONS HELD:

Rear Admiral, USPHS - 1971-1982
(Assistant Surgeon General)

Deputy Director, Bureau of Foods, FDA - 1970-1972

Associate Bureau Director for Toxicological Sciences, Bureau of Foods, FDA - 1972-1982

KA

President, The Nutrition Foundation, Inc.
Washington, DC - 1982-1984

PRESENTATIONS AND PUBLICATIONS:

Over 100 invited speeches and published papers concerning the safety of chemicals and foods, animals and human nutrition, and public policy issues and law.

(Detailed bibliography to be provided upon request.)

KA

COPY

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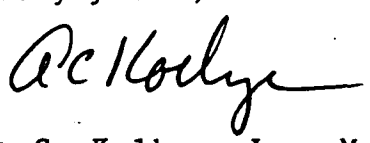
October 31, 1990

Public Docket A-90-16
Air Docket (LE-131)
EPA 401 M Street, SW
Room M-1500
Washington, DC 20460

Dear Sir/Madam:

On behalf of Chemetals, Inc. (711 Pittman Road, Baltimore, MD 21226), enclosed are additional comments on the waiver request of Ethyl Corporation for the use of HiTEC 3000 in unleaded gasoline in the United States.

Sincerely yours,



Albert C. Kolbye, Jr., M.D., M.P.H., J.D.
Director, Kolbye Associates

ADDENDUM FROM KOLBYE ASSOCIATES CONCERNING MANGANESE IN AIR

During a recent meeting (19 October 1990) between Chemetals, Inc. and EPA officials, the latter raised several questions of concern to them. This addendum is divided into three parts: manganese levels in air, manganese inhalation studies in non-human primates, and manganese studies on patients with Alzheimer's Disease or other forms of dementia.

MANGANESE LEVELS IN AIR

First was a question of how representative the mean air concentrations of manganese actually were in view of their allegations that some air monitoring stations had picked up to 20 times higher levels. Without knowing their data, it would be expected that from time to time and place to place, higher air levels of manganese can be found.

Explanations are likely to involve proximity to point sources of manganese emissions such as ferromanganese smelting and alloy production sites, welding activities, or airborne ground-dust on windy days.

Welding activities usually involve fumes and such point sources should be controlled for reasons of occupational and environmental health. They are not part of the HiTec3000 consideration, nor are smelters and airborne ground-dust.

Smelters fall into the same category as welding operations and airborne emissions should be properly controlled.

Airborne ground-dust may contain appreciable quantities of manganese but frequently involves relatively large particle sizes greater than 10 microns and hence will not be respirable. If some particles are inhaled very little will remain in the lung as most will be exhaled and much of the remaining residue will be expelled out of the respiratory system by mucociliary activity in the bronchial tubes or nasopharynx and either expectorated or swallowed. In the latter case, very little -under 4%- will be absorbed from the gastrointestinal tract into the mammalian body and when it is, homeostatic mechanisms of control and excretion will take over. Such airborne ground-dust is not relevant to the HiTec3000 considerations; ground-dust has been airborne since time immemorial. There is no record of manganism from such exposures unless very intensive point sources such as mining or smelting are involved.

It is clear that only very negligible amounts of additional airborne manganese will arise from the usage of HiTec3000 in automotive fuels. The additional fraction is estimated to be within a few percent (maximum about 10%) of airborne manganese presently encountered from sources other than HiTec 3000.

If HiTec3000 is used as a fuel additive, automobile exhaust emissions at the "worst case assumptions" level were estimated to approximate 500 nanograms/M3 of actual tailpipe exhaust by the Health Effects Institute.[1] 1500 nanograms/M3 in tailpipe exhaust have been estimated by Ethyl Corporation in the waiver application[2]. These emissions then would immediately be diluted into the local atmosphere. Over a very short time, such dilution would normally be several hundreds or thousands-fold, depending upon air circulation, thus reducing the levels of manganese in air to those approximating ambient ones. Even in the Pennsylvania Turnpike studies during the mid-1970s, the tunnel air contained only an average of 110 nanograms/M3 of manganese. How much was respirable is not given. National Air Surveillance Network data shows that the highest urban air concentration of manganese between 1972 and 1982 was 34 nanograms/M3 and the highest 95th percentile was 120 nanograms/M3.[3] In the same reference, higher levels from 300 to over 1000 nanograms/M3 have been reported near foundries and ferromanganese plants, respectively.

Another consideration has been introduced by EPA in its HAD of 1984: that of particle size in relation to concentration of manganese. "More recent data tend to indicate that less of the ambient manganese is found in fine particles."[4] The text goes on to say that the average percentage of manganese in fine (under 2.5 microns) particles was 28% or in effect, 16% of measured manganese. By implication, except for unusual situations, most of the airborne manganese is in the "coarse" particles ranging from 2.5 to 15 microns. The coarser particles are much less likely to be absorbed through the alveolar membrane into systemic circulation and are more likely to be excreted from the pulmonary tract.[5] Of additional interest is EPA's estimate that: "Alveolar deposition of manganese at current ambient levels is estimated as 0.072 micrograms/day (average) and 6.6 micrograms/day (high). Estimates of total thoracic deposits are slightly higher. Alveolar and total thoracic deposition under high exposure conditions in the 1960s were

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[1] Health Effects Institute report,1988

[2] Assumptions underlying calculations:
5 micrograms Mn/mile emission
25 mpg
2.0 liter engine
2000 rpm
15 inches Hg manifold vacuum

[3] Health Effects Institute,1988 @ p.8

[4] EPA-HAD,1984 @ p.3-74

[5] See discussion in EPA-HAD, 1984 @ pp. 3-83 and 3-84.

estimated to be as high as 100 and 152 micrograms/day, respectively."[6] These estimates refer to ambient air without MMT.

While tailpipe emissions of manganese from vehicles using MMT in HiTec3000 are initially in the lower size range, such residues in air will be diluted very substantially and, by estimate are unlikely to contribute more than a few nanograms to ambient air concentrations of manganese. If automotive emissions of manganese are adsorbed onto the surfaces of larger particles in automotive emissions or in the ambient air, they are far less likely to be respirable and accordingly are far less likely to be absorbed through the alveolar membrane into the human body. When they settle to the ground surface, they will become identical to manganese in ground-dust.

> Conclusion: Of ambient manganese, only a minor fraction is respirable. Of 34 nanograms/M3 in ambient air, probably only 10 nanograms are in the respirable range. Additional respirable manganese added to air from usage of MMT in HiTec 3000 is unlikely to exceed a few nanograms. There should be no problem whatsoever with this negligible addition.

MANGANESE INHALATION STUDIES IN NON-HUMAN PRIMATES

Concern was also raised by EPA about the adequacy of dose-response data from inhalation studies of manganese toxicity. Rodents such as mice, guinea pigs, hamsters and rats all are obligate nose breathers. Consequently their anatomical characteristics of narrow and convoluted nasal turbinates and narrow pulmonary airways are extreme confounding and interfering factors for accurate assessments of inhalation toxicity. Although rodents have been used in large numbers since they are relatively cheap and logistically easy to manage, anatomical and physiological differences can render them irrelevant for particular purposes.

When testing for manganese toxicity, almost all species have many similar behavioral and pathological changes when effective doses are given by whatever route of administration. These include neurotoxicity findings. However, non-human primates have larger airways and more closely resemble humans with regard to naso-pharyngeal and pulmonary anatomy and physiology. In many other ways they also resemble humans much more than do rodents. They are relatively expensive and much more laboratory support is required to perform experiments. Also, some primates such as chimpanzees are in very short supply and subject to higher priorities for testing purposes that benefit society. Hence, fewer primates are tested than rodents and the number of primates per experiment is usually far less than that of rodents.

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[6] EPA-HAD, 1984 @ p. 3-85.

Toxicological experiments conducted in lesser numbers of non-human primates usually have much greater relevance to human health considerations than do rodent studies involving larger numbers of rodents on test. This is especially true with regard to inhalation toxicology because of the anatomical and physiological considerations mentioned earlier.

Under EPA contract, Coulston and Griffin reported in 1976 on "Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys". Rats were also studied. Four male and four female rhesus monkeys were exposed and three more monkeys of each sex served as non-exposed controls. Dietary manganese averaged 47 mg/ gram of monkey chow. Water manganese ranged from 0.17 to 0.33 micrograms/ml. For periods lasting up to 66 weeks, these male and female rhesus monkeys were exposed by inhalation to manganese in air at a concentration of 100 micrograms/M3 (100,000 nanograms/M3) for 23 hours/day. (Rats received similar exposures for up to 8 weeks.) Additionally, two rhesus monkeys were exposed by inhalation to 5 mg/M3 (5000 micrograms/M3 or 5,000,000 nanograms/M3) of manganese in air for 23 hours/day for 23 weeks and then observed for an additional 10 months. Excretion of manganese reflected dietary intake, not air intakes. Minor manganese residue accumulation occurred in visceral tissues, and an average of twice-normal residues were detected in the central nervous system. No morphological changes were detected after pathology examination. (Rats accumulated manganese in lung and brain but quickly reverted to normal after removal from exposure for one week.) No adverse effects such as neurological disorders in the animals were noted. The source of airborne manganese exposure was MMT combusted in air by natural gas.[7]

> Conclusion: At 1000 and 50,000 times expected human exposure under worst environmental conditions (assumed to approximate 100 nanograms/M3 of manganese in air including from MMT) no effects other that slight tissue accumulation and increased excretion were noted in rhesus monkeys exposed by inhalation for substantially long periods of time.
>
> If combusted MMT were involved as a source for human exposure to manganese, comparable test exposures in this experiment for respirable manganese would still have been the same because the assumption for this author's analysis of potential human exposure was a high estimate of 100 nanograms/M3 of total manganese. Actually the respirable portion of the total particulate average

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[7] "Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys, EPA contract 68-02-0710, reported in November, 1976 by Frederick Coulston, Ph.D. and Travis Griffin, Ph.D. of Albany Medical College and Holloman Air Force Base, New Mexico.

ambient range of 34 nanograms/M3 average manganese residues in air is about 10 nanograms/M3 without MMT usage. With MMT usage, a reasonable estimate is an additional few nanograms/M3 of respirable manganese, which is still very far below the conservative estimate of 100 nanograms used for this analysis. Thus, the actual experimental dosage margins approximated 10,000 and 500,000 times anticipated human exposure to respirable manganese in air including MMT usage. While some tissue accumulation of manganese in rhesus monkeys did occur, there were no discernible pathological effects seen, including neurobehavioral. Granted that these were not lifetime exposures, but the exposures were of sufficient duration, frequency and intensity that if pathological findings were to occur, they should have been noticed under these experimental conditions. **When normal safety factors of 100[8] are used for a non-carcinogenic substances, we can see that we have a safety margin approximating 100 to 5000 times the normal safety margin of 100.**

Squirrel monkeys (32) were divided into four groups, each containing 4 males and 4 females.[9] One group served as controls and the other three were exposed 24 hours/day to inhaled manganese from MMT combusted in propane resulting in manganese air concentrations of 10, 100, and 1000 micrograms/M3. Half the monkeys were exposed for 9 months and then sacrificed; the remaining monkeys were observed post-exposure for an additional 6 months prior to sacrifice and examination. No adverse effects related to manganese exposure were reported. Extensive clinical, laboratory and pathology examinations were conducted including tissue residue studies. No problems were encountered.

Conclusion: In a different species of non-human primate, again no adverse effects were noted at the doses studied. **These inhalation exposures to manganese that caused no adverse effects in squirrel monkeys were at 100, 1000 and 10,000 times greater than anticipated human exposures at**

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[8] The U.S. Food & Drug Administration uses a safety factor of 100 times the highest no-adverse effect level for lifetime studies in rodents administered the test compound. Even though the non-human primate studies were less-than-lifetime, their relevance to human health considerations are far higher than dose-response data generated from studies in rodents. Even if we subtracted a factor of 10 to allow for subtle adverse effects, we still see very substantial safety margins.

[9] Huntingdon Research Center 1975 report to Ethyl Corporation, Project Number 731-339.

worst case, if 100 nanogram/M3 is used as an assumption. This assumption includes usage of MMT.

The two studies of the effects of combusted MMT in monkeys are notable for many reasons. The animals were directly exposed to manganese from combusted MMT, so that particle size conditions referable to human exposure were duplicated. Their airways, lungs and central nervous systems closely mimic human counterparts.

No adverse pathology or neurobehavioral changes were noted although some tissue accumulation was noted in extremely high dose exposure conditions. These are not relevant to the levels of anticipated human exposure in non-occupational settings.

MANGANESE STUDIES ON PATIENTS WITH ALZHEIMER'S DISEASE OR OTHER FORMS OF DEMENTIA

It is well known that aluminum and silicon are more highly concentrated in the neurofibrillary tangles that comprise the microscopic lesions noted in the brain tissues of patients with Alzheimer's Disease. Whether these are causes or associated effects is not known because the etiologic factors that cause this disease are not completely understood; a viral etiology has not been excluded as the primary cause. But manganese has been studied in relation to these diseases and to other forms of dementia. No significant differences in manganese concentration levels in brain tissues of Alzheimer's patients were noted in three different reports by Markesbery et al (1984)[10], Shore et al (1984)[11], and Hershey et al (1983)[12]. While chronic manganism is known to be associated with brain disease similar to Parkinson's Syndrome, there is no credible evidence that manganese is contributing to dementia in the elderly.

SUMMARY: The concentrations of manganese in air are not significantly increased from usage of MMT in HiTec3000. Non-human primates tolerate long-term exposures to combusted MMT very well. No linkage has been established between manganese and the dementias of the elderly such as Alzheimer's Disease.

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[10] Markesbery et al, Neurotoxicology 5 (1): pp.49-57, 1984.

[11] Shore et al, Journal of American Geriatric Society, 32 (12): pp. 892-895, 1984.

[12] Hershey et al, Neurology 33 (10): pp. 1350-1353, 1983.